REMARKS

The specification on page 1 for this application has been amended solely to introduce acknowledgment of Federal Support of work leading to the invention contained in this application. Thus, no new matter has been introduced by this amendment.

The specification and Figures for this application have been amended in order to comply with the requirements for drawings and application under 37 C.F.R. § 1.75(h); §1.84(o); § 1.84(e) and § 1.821-1.825.

In particular, the drawings have been amended to remove excessive text, and darken and/or improve print quality. The specification has also been amended to reflect these changes to the drawings. In particular, the Brief Description of the drawings has been amended to incorporate the description originally provided as part of the drawings. In addition, the specification has been amended to incorporate appropriate sequence identifiers from the accompanying Sequence Listing. Also, in order to comply with 37 C.F.R. §1.75 (h) substitute pages have been submitted in order to have the claims commence on a separate sheet of paper.

The above made amendments do not introduce new matter to the present application. It is believed that this preliminary amendment does not unduly interfere

with the preparation of the first Office Action for this Application. Accordingly, entry of these amendments is respectfully requested.

Respectfully submitted,

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EXHIBIT 1: AMENDMENTS TO U.S. PATENT APPLICATION SERIAL NO. 09/863,765 (ATTORNEY DOCKET NO. 9373/1H812US3)

SUBMITTED PURSUANT TO 37 C.F.R. § 1.121(b)(1)(iii)

Amend page 1at line 11 of the specification by inserting the following new paragraph which reads as follows:

Work leading to this invention was supported by Grant No. N00014-96-1-0340 awarded by the United States Navy. The United States government may have certain rights to this invention, pursuant to the term of that grant.

Amend the paragraph at lines 24-27 on page 15 of the specification so that the paragraph reads as follows:

FIG. 3 is a gene alignment for β-lactamase-like genes, (1) *Enterobacter cloacae,* **SEQ. ID NO.1**,; (2) *Citrobacter freundii,* **SEQ. ID NO.2**; (3) *Yersinia enterocolitica* , **SEQ. ID NO.3**; *and* (4) *Klebsiella pneumonia*, **SEQ. ID NO.4**. SWISPROT or TrEMBL accession numbers for the protein sequences and GenBank accession numbers for the DNA sequences are given.

The paragraph at lines 1-3 on page 17 of the specification should be amended as follows:

FIG. 7 is an example of an *in vitro* method of overlap extension reassembly, targeting identified crossover locations. The appropriate fragments may be obtained by split-pool synthesis. In **FIG. 7**, part (A), all possible recombinants are

prepared by crossover at positions 1 and 2. In **FIG 7**, part (B), the recombinants can be prepared by assembly of synthetic fragments containing the crossover positions. This example requires fragments (plus end primers).

The paragraph at lines 4-7 on page 17 of the specification should be amended as follows:

FIG. 8, part (A), [**A**]shows a fragment reassembly method using a parental template. The synthetic fragments are extended against a parent template strand and the gaps are repaired. In **FIG. 8**, part (B), t[T]he resulting products are subjected to heteroduplex recombination (Volkov *et al., Nucl. Acids Res.*, 27:18 (1999))to create libraries of genes within regions of non-identity. More complexity can be introduced by the addition of more fragments during template assembly.

The paragraph at lines 8-9 on page 17 of the specification should be amended as follows:

FIG. 9 shows the preparation of gene fragments prepared by PCR with primers directed to regions targeted for crossovers. In **FIG. 9**, part (A), the fragments are prepared by PCR with primers. The PCR reactions are performed with primers 1 + 2, 3 + 4 and 5 + 6. The method is repeated for the other parents.

The paragraph at lines 10-11 on page 17 of the specification should be amended as follows:

FIG. 10 shows recombination directed to specific sites using crossover primers in DNA shuffling. In **FIG. 10**, part (A), crossover primers designed to have crossovers at designated positions (2 primers for each position) are prepared. In **FIG. 10**, part (B), the parent genes are fragmented and reassembled , utilizing PCR methods, in the presence of the crossover primers to promote recombination at designated positions.

The paragraph at lines 14-15 on page 17 of the specification should be amended as follows:

FIG. 12 is a flow diagram illustrating one embodiment of a recombinant search algorithm of the invention, based upon sequence identity. In **FIG. 12**, part (1), the parent sequences are aligned with the template structure. In **FIG 12**, part (2), all possible crossover points are determined according to a sequence identity algorithm. In **FIG. 12**, part (3), the coupling matrix is calculated. In **FIG. 12**, part (4), a start parent is picked at random and copied to the offspring until a possible cut point is reached. In **FIG. 12**, part (5), a random number is picked, and if the number is less than p, a random new parent is copied until the next cut point is reached. In **FIG. 12**, part (6), the crossover disruption of the offspring gene is determined.

The paragraph at line 16-26 on page 26 of the specification should be amended as follows:

FIG. 19 is a schematic demonstrating the utility of a contact map in identifying compact units of substructure. A representative contact map is on the left. The graph on the right is a statistical study of the average length of contiguous residues that can fold into a sphere of the indicated diameter (Gilbert 1998). This information can be used in the following way. If a 15-residue segment can fold into a sphere with a diameter of 21 angstroms, then this segment could be considered as being of average compactness. However, if a 20-residue segment can fold into a sphere of 21 angstroms, this is considered as having a significantly above-average compactness. This is visualized on the contact map as a triangle on the diagonal formed by the cut points required to generate the segment. If the segment fits into a sphere of the specified diameter, then the triangle will be entirely white (interacting). The contact map shows residues that are distant (black) and residues that are close (white). If a given segment, ▬▬, folds an above average number of residues into a given sphere size, then it is compact.

Please amend the specification at page 122, line 21, as indicated in the accompanying Exhibit 1, so that the paragraph reads as follows:

To test our ability to predict crossover locations, we designed experiments to recombine fragments of two beta-lactamases, TEM-1 and PSE-4, using

the SOEing procedure to piece together fragments by PCR (Horton, R. M., (1995) *Mol. Biotech.* 3, 93-99). While the proteins in this example have only 40% amino acid sequence identity, they share similar structures (TEM-1 , SEQ ID NO: 5; and PSE-4 SEQ ID NO: 6) (Jelsch, C., Mourey, L., Masson, J. M., & Samama, J. P., (1993) *Proteins* 16, 364; Lim, D., Sanschagrin, F., Passmore, L., De Castro, L., Levesque, R. L., & Strynadna N. C. J., (2001) *Biochemistry* 40, 395).